

RESEARCH ARTICLE

The Impact of Malarone® and Primaquine on Psychomotor Performance

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The impact of Malarone® and primaquine on psychomotor performance. Aviat Space Environ Med 2003; 74:738-45.

Introduction: Recent evidence has established the effectiveness of Malarone® and primaquine for chemoprophylaxis against *Plasmodium falciparum* malaria. Both have the advantage of providing causal prophylaxis and therefore require continued dosing for only 1 wk after departure from a malaria endemic area. Canadian Forces aircrews are often placed in situations that put them at risk for malaria infection but the safety of these drugs for use in aircrew has not been ascertained. This study was undertaken to determine whether or not Malarone or primaquine impact psychomotor performance. **Method:** Twenty-eight subjects (20 men and 8 women) ranging from 21 to 52 yr of age were assessed for psychomotor performance on 2 psychomotor test batteries at the end of a 7-d dosing protocol for each of placebo, Malarone, and primaquine treatment, in a double-blind crossover design with counter-balanced treatment order. All subjects were also assessed for psychomotor performance once per week during the 3-wk washout intervals. The daily Malarone dose was atovaquone 250 mg/proguanil 100 mg and the daily primaquine dose was 30 mg of base. In order to verify subject compliance with the medication dosing protocol, blood samples were drawn from all subjects at the end of each of the three 7-d loading protocols. All three medications were packaged in identical gelatin capsules for blinding purposes. At each psychomotor test session, all subjects completed a drug side-effect questionnaire, a mood questionnaire, and a sleepiness/fatigue questionnaire. **Results:** There was no significant impact of Malarone or primaquine on serial reaction time, logical reasoning, serial subtraction, or multitask performance. With respect to drug adverse effects there were no significant main effects or interactions for the documented adverse effects of these medications (abdominal cramps, epigastric distress, nausea, vomiting, anorexia, headache, coughing and dizziness). **Conclusions:** There was no impact of either Malarone or primaquine on psychomotor performance, mood, sleepiness, or fatigue. The usual adverse effects of these medications were not significantly manifested in our subjects. These findings support the possible use of either Malarone or primaquine in aircrew for malaria chemoprophylaxis.

Keywords: Malarone, primaquine, aircrew, adverse effects, psychomotor performance.

MALARIA INFECTS more than 300 million people around the world, killing over 3 million annually (10,23). Malaria is a common and serious infection caused by four species of the genus *Plasmodium*: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*. Infection with *P. falciparum* can be fatal, and infections caused by *P. vivax* and *P. ovale* can relapse from latent liver stages. All species of malaria are transmitted by the bite of an infected female *Anopheles* mosquito. Rarely, transmission may occur by blood transfusion, by shared needle use, or congenitally from mother to fetus. The disease is characterized

by fever and flu-like symptoms such as myalgias, headache, abdominal pain, and malaise. Rigors and chills often occur. The classically described alternate-day fevers or other periodic fevers are often not present. Severe malaria due to *P. falciparum* may cause seizures, coma, and renal and respiratory failure, and may lead to death. Malaria deaths are frequently the result of delays in the diagnosis and treatment of the infection. The widespread resistance of *P. falciparum* to chloroquine has complicated the prevention and treatment of malaria. Drug-resistant strains of malaria are now common in much of the world.

Canada has one of the highest rates of imported malaria among industrialized countries, with 400 to 1000 cases annually, a per capita rate up to 5 times that of the U.S. (7,15). "Every case of malaria is a public health failure, and every death from malaria is a major medical failure" (16). Annually, 30 to 40 cases of imported malaria are reported in U.S. military personnel, with approximately 10 of these cases occurring in aircrew (15). If this pattern is similar in Canadian troops, the increasing number of cases of imported malaria may soon be a serious problem. Canadian Forces (CF) aircrew are often placed in situations that put them at risk for malaria infection. Further, the limited choice of malaria chemoprophylaxis for aircrew is not optimal. Failure to prevent malaria in this population could have adverse consequences, both for the individual aircrew member as well as for passengers or those on the ground if malaria symptoms occur while piloting an aircraft. Another concern is that aircrew are at risk of contracting a potentially life-threatening disease in geographic locations in which safe or effective therapy may not be available. Although aircrew have more restrictions with respect to medication use, non-aircrew CF personnel are increasingly being deployed

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This manuscript was received for review in October 2002. It was revised in January 2003. It was accepted for publication in February 2003.

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to areas of the world endemic for malaria and it is preferable that they all receive chemoprophylaxis with minimal adverse effects on psychomotor performance. Essentially, while there is concern with the issue of malaria prevention in aircrew, there is also concern with possible adverse effects from malaria chemoprophylaxis.

During World War II, the United States government supported a research program that tested over 16,000 compounds for antimalarial activity. The most promising of these compounds were not further developed because of phototoxicity in humans. In response to the Vietnam conflict, the most promising of these previously phototoxic compounds was further developed to the point where it was still 90% efficacious in malaria treatment and prophylaxis but free of phototoxic effects. This compound became known as mefloquine (Lariam®) and was first used in clinical trials in 1975 (13). Most of the currently recommended malaria prevention regimens have some psychomotor performance adverse effects (2,4,14,18,24,28). One (mefloquine) is banned altogether in aircrew because of potential adverse effects on spatial-motor coordination (10); this despite a flight simulator study of Swiss pilots which demonstrated good tolerance and failed to reveal adverse drug effect on simulated pilot performance (25), and another study which failed to demonstrate an effect on driving performance (30). In addition, compliance with a chemoprophylactic regimen is an issue, particularly if prolonged medication use is required for brief (yet recurring) or extended operations. Aircrew often fall into the former group and previous work suggests that compliance can be a large problem in this type of tasking (26).

At present, CF pilots receive either chloroquine or doxycycline for malaria prevention prior to departing to a malaria endemic area. Chloroquine is a well-tolerated drug with a weekly dosage, which usually gives a high compliance to the medication (3), but because of the emergence of chloroquine-resistant *falciparum* malaria, this is no longer a drug of choice in most malaria endemic areas of the world. Historically, when pilots travel through areas with chloroquine-resistant *Plasmodium falciparum*, doxycycline has been recommended for chemoprophylaxis. The main disadvantage of this regimen is the essential adherence to daily dosing, gastrointestinal adverse effects, induction of cutaneous photosensitivity, and the necessity to continue chemoprophylaxis for 4 wk after departing from malaria endemic areas. Compliance is potentially further compromised due to the CF requirement for aircrew to make frequent short duration sorties through malaria endemic areas.

Recent evidence has established the effectiveness of Malarone® (GlaxoSmithKline, Research Triangle Park, NC) (27) and primaquine (3) for chemoprophylaxis against *P. falciparum* malaria. Both have the advantage of providing causal prophylaxis and therefore require continued dosing for only 1 wk after departure from a malaria endemic area. Thus, the efficacy of these agents for malaria prevention has been established (3,7,26,27), but the utility of these drugs in aircrew cannot be

ascertained until the lack of effect on psychomotor response has been further studied. To date there has been only one study that tested for neuropsychiatric adverse events due to Malarone (29). There are none for primaquine. The Malarone study (29) did not assess aviation-relevant performance to address possible flight safety issues with the use of this medication in aircrew.

Malarone

Malarone is a fixed drug combination (tablet: 250 mg atovaquone and 100 mg proguanil) recently licensed in Canada for prevention of malaria, and licensed since 2000 for treatment of uncomplicated *P. falciparum*. The United States FDA approved it in the summer of 2000 for the prevention and treatment of malaria in adults and children (7).

Atovaquone combined with proguanil, used to treat malaria, results in cures in 98.7% of the patients with uncomplicated *P. falciparum* (7). Compared with other standard antimalarial treatment regimens, the atovaquone/proguanil combination has demonstrated excellent safety and tolerance with fewer reported adverse events than mefloquine or quinine plus tetracycline (27). Results using Malarone as a chemoprophylactic agent in semi-immune and non-immune individuals (travelers) have demonstrated 98% efficacy in preventing *P. falciparum* (7). The elimination half-lives of atovaquone and proguanil are about 2 to 3 d and 12 to 21 h respectively. As listed in the product monograph, after a single dose, the C_{max} for the components of Malarone are $11.5 \mu\text{g} \cdot \text{mL}^{-1}$, $509 \text{ ng} \cdot \text{mL}^{-1}$, and $44 \text{ ng} \cdot \text{mL}^{-1}$ for each of atovaquone, proguanil, and cycloguanil (a primary metabolite of proguanil) while the corresponding T_{max} values are 11, 8, and 7.5 h respectively.

The most common adverse effects reported while receiving treatment with atovaquone are: rash, nausea, diarrhea, headache, vomiting, abdominal pain, and insomnia. The most common adverse effects reported while receiving treatment with proguanil are: anorexia, nausea, vomiting, abdominal pain, diarrhea, mouth ulcers, stomatitis, and headache. There has been no evidence of increased toxicity following concurrent administration of the two compounds. At the doses employed for the treatment of malaria, adverse reactions have generally been mild and of limited duration. Of the seven severe or treatment limiting adverse experiences reported in clinical trials with atovaquone and proguanil, three were considered to be treatment related, two were reports of nausea and/or vomiting, and one was a report of an anaphylactic reaction.

Primaquine

Primaquine has been used for decades to prevent relapses of *P. vivax* and *P. ovale* infections and because of its activity against the hypnozoite and developing liver stages of malaria, it can eliminate infections that are developing in the liver. This is termed causal prophylaxis.

Recent studies indicate that primaquine appears to be a safe and effective prophylactic agent that is better tolerated than other standard chemoprophylaxis with a

protective efficacy of 85%–95% against both *P. falciparum* and *P. vivax* infection (3). Theoretically, because primaquine is a causal agent, individuals need only take it during periods of exposure and for 1 wk after departure from the malaria endemic area. It is known that failure of completion of post-exposure chemoprophylaxis is a common reason for non-adherence with standard regimens. Therefore it may be particularly useful for travelers with short exposures (2–7 days) in high-risk areas (3). Primaquine has an elimination half-life of 6 h. As listed in the Micromedex index the C_{max} value for primaquine after a 30 mg dose is 80 ng · mL⁻¹. The primary metabolite of primaquine is 8-(3-carboxyl-1-methylpropylamino)-6-methoxyquinoline that after a single dose, results in 10 times higher concentrations than the parent molecule but which has much less antimalarial activity than the parent molecule. Further, this metabolite is eliminated more slowly than the parent compound and thus accumulates with chronic dosing. The T_{max} values for primaquine and its primary metabolite (8-(3-carboxyl-1-methylpropylamino)-6-methoxyquinoline) are 1 to 3 h and 3 to 12 h respectively.

The most common adverse effects reported while receiving treatment with primaquine are gastrointestinal (nausea, vomiting, epigastric distress, and abdominal cramps), and hematologic such as leukopenia (low white blood cell count) or hemolytic anemia (rupturing of red blood cells). The latter adverse event occurs in glucose-6-phosphate dehydrogenase (G6PD) deficient individuals and may be severe or even fatal. Therefore, use of primaquine mandates prior G6PD testing.

The present protocol is designed to evaluate the impact of Malarone and primaquine at steady-state levels on psychomotor performance, to assess the impact of these two medications on mood, and to monitor adverse effects.

METHODS

Study Design

The design was a repeated-measures double blind cross over protocol with three drug conditions: Malarone, primaquine, and placebo. Each of the three medication courses involved a 7-d loading protocol, each separated by 3 wk in order to allow for drug washout. The order of medications was counterbalanced across subjects. The Malarone course required a single daily dose of one tablet (atovaquone 250 mg/proguanil 100 mg), and the primaquine course also involved a single daily dose (2 tablets, each of 15 mg base). The subjects were instructed to take their medications each morning with food for 7 consecutive days. The study medications were prepared by a contract pharmacy and were placed in identical single capsules for blinding purposes. Each capsule contained the appropriate daily dose for each study arm (i.e., Malarone, primaquine, or placebo).

Subjects

This study protocol was approved by the DRDC-Toronto Human Research Ethics Committee (HREC).

The subjects were 28 volunteers (military and civilian) from the Toronto laboratories of Defense Research and Development Canada, aged between 18 and 52 yr who provided written informed consent. One subject withdrew from the study after breaking an arm in a motor vehicle accident. Before being accepted into the study, all volunteers first passed a screening medical designed to preclude participation by any subjects for whom Malarone or primaquine would be contraindicated and to disqualify any subjects with mental or physical problems. Because Malarone or primaquine could be potentially harmful to a fetus, any female who wished to participate was required to undergo pregnancy testing as part of medical screening. Further, all female subjects were advised to take precautions to avoid pregnancy during this study as well as during the 3 mo following completion of the study. The exclusion criteria included the following:

- history of seizure disorder,
- known allergy or sensitivity to either drug,
- glucose-6-Phosphate dehydrogenase deficiency (primaquine),
- use of malarial prophylaxis within 2 mo prior to commencement of the study,
- lactating women,
- pregnancy or intention to become pregnant within 3 mo after taking part in the study,
- medication which might impact on psychomotor performance.

In order to avoid contaminating psychomotor results, subjects abstained from the use of hypnotics or tranquilizers from 2 wk before any psychomotor testing, and from alcohol within 12 h before psychomotor testing. Subjects were not restricted from their normal daily intake of caffeine containing beverages or from normal daily exercise routines. The medications were administered by the principal investigator or his designate in accordance with the dosing protocol established by our contract pharmacy (Central Medical Pharmacy, Toronto, Canada). In order to verify compliance with study medication dosing protocol, at the end of each of three 7-d loading protocols (Malarone, primaquine, and placebo), blood samples were drawn immediately after the psychomotor test session (i.e., on three occasions for each subject). The blood samples were drawn by a physician or by a qualified and physician-approved technician. The Center for Disease Control (CDC) in Atlanta assayed the blood samples for levels of each drug and primary metabolite by high performance liquid chromatography.

Procedures

Prior to commencement of the study, all subjects were fully trained on both psychomotor tests batteries by performing a minimum of 12 iterations of each of the 2 task batteries: 1) a subset of the DRDC Toronto sustained operations battery (SUSOPS) to measure serial reaction time (SRT) (32), logical reasoning (LRT) (1), and serial subtraction task (SST) (9) performance, and 2) a recently developed multitask (MT) (31) designed to

Impact of Malarone and Primaquine on SRT Performance

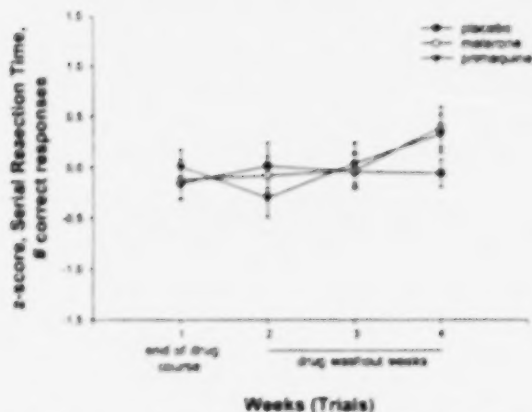


Fig. 1. z-scores for number of correct responses to the serial reaction time task. All values are mean $\pm$ SEM and are plotted across drugs and weeks.

simulate the information processing characteristics of flight performance and which generates scores related to error detection and selective attention, visuo-motor tracking and coordination, short-term memory, mental arithmetic, and scanning strategies. The MT was developed during approximately 8 mo of study and observation of flight simulators, including the Airbus 310, the Boeing 747, and the Cessna Citation. This laboratory has used the MT numerous times; once in an aircrew fatigue study (22) and in three studies to evaluate drug effects on psychomotor performance (19–21). All psychomotor tasks were administered from laptop computers in a psychomotor test suite with a controlled environment and with individual cubicles in order to preclude any distractions during psychomotor testing. Because the capacity of the psychomotor test suite is

Impact of Malarone and Primaquine on LRT Performance

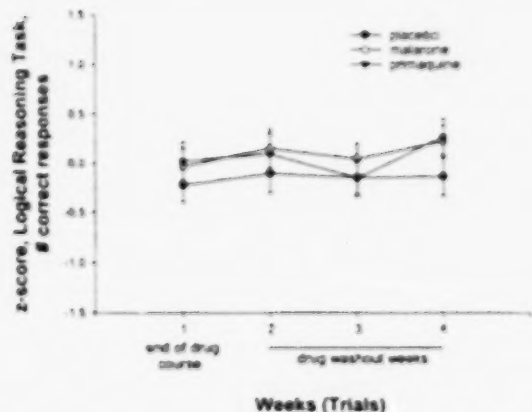


Fig. 2. z-scores for number of correct responses to the logical reasoning task. All values are mean $\pm$ SEM and are plotted across drugs and weeks.

Impact of Malarone and Primaquine on SST Performance

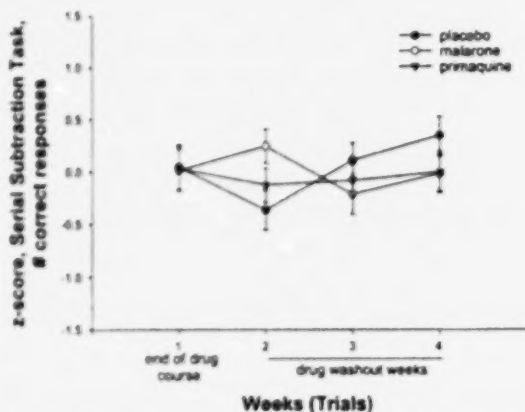


Fig. 3. z-scores for number of correct responses to the serial subtraction task. All values are mean $\pm$ SEM and are plotted across drugs and weeks.

five subjects, all subjects were run in syndicates of up to five persons only. The three SUSOPS tasks took 10 min to complete (1 min for a subjective sleepiness/fatigue questionnaire followed by 3 min of SRT, 3 min of LRT, and 3 min of SST which has an imbedded short term memory component). The SUSOPS battery has been used extensively in psychomotor performance studies for over three decades. The SUSOPS task battery was followed by the MT which took 15 min to complete and which involved tracking toward various targets (way-points) while attending to a flight director, monitoring attitude indicators for discrepancies, remaining vigilant for altitude command changes, and operating a tracking task analogous to the operation of the power quadrant of a large multi-engine transport aircraft. One trial of both task batteries (all four tasks) takes 25 min to complete. During the study, all the subjects were as-

Impact of Malarone and Primaquine on Multitask Performance

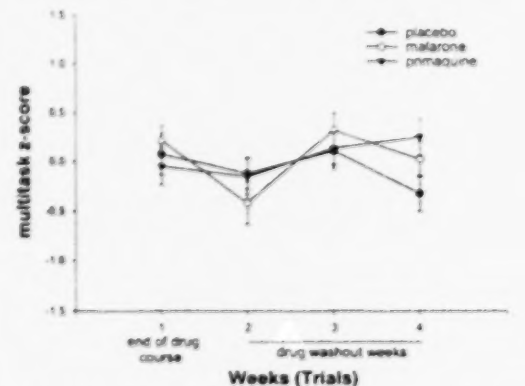


Fig. 4. z-scores for multitask score. All values are mean $\pm$ SEM and are plotted across drugs and weeks.

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TABLE I. SUBJECTIVE SLEEPINESS AND FATIGUE SCORES ACROSS WEEKS FOR PLACEBO, MALARONE, AND PRIMAQUINE.

	Week 1	Week 2	Week 3	Week 4
	For each cell: top line = placebo; middle line = Malarone; bottom line = primaquine.			
Sleepiness	2.22 ± 0.18	2.15 ± 0.21	2.19 ± 0.22	2.11 ± 0.15
	2.26 ± 0.21	2.15 ± 0.18	2.30 ± 0.24	2.37 ± 0.19
	2.22 ± 0.17	2.26 ± 0.21	2.19 ± 0.13	2.30 ± 0.21
Mental fatigue	2.51 ± 0.27	2.31 ± 0.22	2.59 ± 0.29	2.43 ± 0.26
	2.56 ± 0.28	2.36 ± 0.27	2.51 ± 0.29	2.47 ± 0.26
	2.48 ± 0.25	2.53 ± 0.27	2.50 ± 0.23	2.60 ± 0.31
Physical fatigue	2.33 ± 0.26	2.19 ± 0.20	2.52 ± 0.27	2.40 ± 0.25
	2.55 ± 0.27	2.35 ± 0.26	2.48 ± 0.27	2.36 ± 0.23
	2.42 ± 0.25	2.52 ± 0.25	2.42 ± 0.20	2.35 ± 0.26

All values are mean ± SEM. Score scales ranged from 1 to 7 with higher numbers indicating more sleepiness/fatigue.

sessed for psychomotor performance on day 7 of each medication course. The medication courses were staggered so that the seventh (and final) day of the medication protocol generated a morning psychomotor test syndicate (at 1030 h) and an afternoon psychomotor test syndicate (at 1430 h) on Tuesday, Wednesday, or Thursday. Each time the subjects underwent a psychomotor performance test session, they were asked to complete a questionnaire soliciting their subjective responses to queries regarding any medication-induced adverse effects as well as a questionnaire soliciting subjective responses to queries designed to facilitate quantification of their mood (U.S. Naval Health Research Center

Mood Scale) (12). In order to maintain psychomotor skill, all subjects underwent weekly psychomotor testing during the 3-wk washout periods between drug arms as well for 3 wk after the last drug arm. In addition to maintaining psychomotor skills during the study, the psychomotor data was collected during washout periods in order to determine if or when any initial performance decrement at the end of the 7-d drug loading periods would recover during washout. The psychomotor test times during drug washout were kept constant for each subject; i.e., the same test day of the week and same test time as at the end of the 7-d loading protocol.

TABLE II. ADVERSE EFFECTS QUESTIONNAIRE SCORES ACROSS WEEKS, FOR PLACEBO, MALARONE, AND PRIMAQUINE.

	Week 1	Week 2	Week 3	Week 4
	For each cell: top line = placebo; middle line = Malarone; bottom line = primaquine.			
severity of abdominal cramps	1.43 ± 0.18	1.15 ± 0.09	1.04 ± 0.04	1.07 ± 0.05
	1.63 ± 0.19	1.07 ± 0.07	1.00 ± 0.00	1.00 ± 0.00
	1.33 ± 0.17	1.04 ± 0.04	1.07 ± 0.05	1.22 ± 0.16
severity of headache	1.26 ± 0.11	1.00 ± 0.00	1.11 ± 0.08	1.30 ± 0.19
	1.30 ± 0.29	1.19 ± 0.08	1.19 ± 0.11	1.15 ± 0.09
	1.48 ± 0.17	1.41 ± 0.21	1.11 ± 0.08	1.07 ± 0.05
severity of nausea	1.19 ± 0.12	1.07 ± 0.07	1.04 ± 0.04	1.15 ± 0.12
	1.48 ± 0.22	1.15 ± 0.12	1.00 ± 0.00	1.00 ± 0.00
	1.20 ± 0.12	1.22 ± 0.13	1.03 ± 0.04	1.07 ± 0.05
severity of diarrhea/loose stools	1.24 ± 0.09	1.11 ± 0.06	1.06 ± 0.04	1.07 ± 0.05
	1.52 ± 0.20	1.22 ± 0.12	1.19 ± 0.19	1.00 ± 0.00
	1.26 ± 0.10	1.07 ± 0.05	1.07 ± 0.05	1.11 ± 0.08
severity of vomiting	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.04 ± 0.04
	1.15 ± 0.10	1.04 ± 0.04	1.07 ± 0.07	1.04 ± 0.04
	1.04 ± 0.04	1.22 ± 0.15	1.04 ± 0.04	1.00 ± 0.00
severity of anorexia, loss of appetite	1.04 ± 0.04	1.00 ± 0.00	1.00 ± 0.00	1.04 ± 0.04
	1.26 ± 0.17	1.04 ± 0.04	1.00 ± 0.00	1.00 ± 0.00
	1.26 ± 0.13	1.04 ± 0.04	1.17 ± 0.12	1.14 ± 0.12
severity of epigastric distress, upset stomach	1.31 ± 0.12	1.07 ± 0.05	1.04 ± 0.04	1.11 ± 0.08
	1.44 ± 0.17	1.15 ± 0.12	1.00 ± 0.00	1.04 ± 0.04
	1.28 ± 0.11	1.19 ± 0.09	1.07 ± 0.05	1.11 ± 0.08
severity of dizziness	1.00 ± 0.00	1.04 ± 0.04	1.00 ± 0.00	1.00 ± 0.00
	1.19 ± 0.11	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
	1.15 ± 0.09	1.07 ± 0.05	1.03 ± 0.04	1.19 ± 0.15
severity of cough	1.26 ± 0.15	1.15 ± 0.09	1.04 ± 0.04	1.02 ± 0.02
	1.37 ± 0.19	1.41 ± 0.18	1.26 ± 0.16	1.26 ± 0.10
	1.31 ± 0.14	1.15 ± 0.07	1.35 ± 0.19	1.24 ± 0.12

All values are mean ± SEM. Score scales ranged from 1 to 7 with higher scores indicating more pronounced adverse effects.

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TABLE III. PREVALENCE OF ADVERSE EFFECTS (PERCENT OF SUBJECTS REPORTING AN ADVERSE EFFECT) ACROSS WEEKS, FOR PLACEBO, MALARONE, AND PRIMAQUINE.

	Week 1 For each cell:	Week 2 top line = placebo;	Week 3 middle line = Malarone;	Week 4 bottom line = primaquine.
abdominal cramps	21.4 39.3 17.9	10.7 3.6 3.6	3.6 0.0 7.1	7.1 0.0 7.1
headache	17.9 25.0 32.1	0.0 17.9 17.9	7.1 10.7 7.1	14.3 10.7 7.1
nausea	10.7 21.4 10.7	3.6 7.1 10.7	3.6 0.0 3.6	7.1 0.0 7.1
diarrhea/loose stools	21.4 25.0 21.4	10.7 14.3 7.1	7.1 3.6 7.1	7.1 0.0 7.1
vomiting	0.0 7.1 3.6	0.0 3.6 7.1	0.0 3.6 3.6	0.0 3.6 0.0
anorexia, loss of appetite	3.6 10.7 17.9	0.0 3.6 3.6	0.0 0.0 7.1	3.6 0.0 7.6
epigastric distress, upset stomach	21.4 28.6 17.9	7.1 7.1 14.3	3.6 0.0 7.1	7.1 7.1 7.1
dizziness	0.0 10.7 10.7	3.6 0.0 7.1	0.0 0.0 3.6	0.0 0.0 7.1
cough	10.7 14.3 17.9	10.7 21.4 14.3	3.6 14.3 17.9	3.6 21.4 14.3

Any score from 2 to 7 was considered to be an occurrence.

Statistical Analysis

The dependent variables (number of correct responses for the SUSOPS tasks and total score for the multitask) were compared across drug conditions. The dependent variables from the questionnaires were also compared across drug conditions. Both the psychomotor and questionnaire data were submitted to repeated-measures analysis of variance. The least significant difference test was used for post hoc assessment of any main effects or interactions. The significance level was set at 0.05.

RESULTS

Psychomotor Data

For all psychomotor data, week 1 corresponds to the end of the 7-d drug loading course while weeks 2 through 4 are drug washout weeks. All psychomotor data sets were submitted to a two-way repeated measures analysis of variance with three levels of 'drug' and four levels of 'trials' (weeks). A completely repeated-measures analysis of variance reduces overall variability by removing between-subject differences from the error term. Note that Figs. 1-4 are graphed in z-scores in order to better demonstrate the within subjects treatment effects. The analyses of variance were equivalent whether done with z-scores or with original units.

The analyses of variance for SRT (Fig. 1), LRT (Fig. 2),

SST (Fig. 3), and the MT (Fig. 4), indicate there are no significant main effects of interactions for any of these tasks. Essentially, neither Malarone nor primaquine impacts performance for any of our tasks.

Subjective Sleepiness and Fatigue Data

The Stanford sleepiness scale data and the mental and physical fatigue data are illustrated in Table I. The analyses of variance for these data indicate no significant main effects or interactions. There is no impact of either Malarone or primaquine on subjective levels of sleepiness, mental fatigue, or physical fatigue.

Subjective Adverse Effect Data

The data illustrating the severity of the nine most common adverse effects attributable to Malarone and primaquine are illustrated in Table II. The analyses of variance for these data indicate a significant main effect of weeks for abdominal cramps ($F(3,78) = 9.23$ $p < 0.00003$), headache ($F(3,78) = 7.06$ $p < 0.0003$), nausea ($F(3,78) = 4.35$ $p < 0.007$), and diarrhea ($F(3,78) = 8.22$ $p < 0.00008$). Post hoc testing of these four main effects of weeks reveals that the severity of these four adverse effects (abdominal cramps, headache, nausea, and diarrhea) is marginally higher in week 1 (i.e., on the last day of the 7-d drug loading protocol) than during

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TABLE IV. SUBJECTIVE MOOD SCORES (U.S. NAVY HEALTH RESEARCH CENTER MOOD SCALE) ACROSS WEEKS FOR PLACEBO, MALARONE, AND PRIMAQUINE.

	Week 1	Week 2	Week 3	Week 4
	For each cell: top line = placebo; middle line = Malarone; bottom line = primaquine.			
Positive mood score	26.19 ± 1.18 27.96 ± 1.34 26.59 ± 1.34	27.74 ± 1.40 28.15 ± 1.22 26.37 ± 1.49	27.56 ± 1.37 26.78 ± 1.21 27.59 ± 1.37	27.22 ± 1.33 26.85 ± 1.18 27.56 ± 1.36
Negative mood score	-10.67 ± 0.56 -11.22 ± 0.51 -10.56 ± 0.52	-10.85 ± 0.47 -10.37 ± 0.51 -10.52 ± 0.53	-10.85 ± 0.46 -10.41 ± 0.51 -10.30 ± 0.54	-10.04 ± 0.51 -10.26 ± 0.52 -10.59 ± 0.46

All values are mean ± SEM.

the washout weeks (weeks 2–4). There were no significant main effects or interactions for vomiting, anorexia, epigastric distress, dizziness, or coughing. While a few subjects had the odd complaint across the various adverse effects, the limited frequency of such complaints was not enough to provoke statistically significant drug effects. The data illustrating the prevalence of adverse effects (percent of subjects reporting each effect) are illustrated in Table III. The data show the frequency of occurrence across subjects, but unlike the data in Table II, the Table III data does not quantify severity of occurrence.

Subjective Mood Data

Both the positive and negative mood data from the U.S. Naval Health Research Center Mood Scale are illustrated in Table IV. The analyses of variance for these data indicate no significant main effects or interaction, thus confirming that neither Malarone nor primaquine have significant mood effects.

Compliance Bloodwork

The CDC blood assays confirmed that all subjects were compliant for the Malarone dosing, but suggested that one subject may not have been compliant with the primaquine dosing protocol. When confronted with this possibility, the subject in question presented us a personal log of his drug ingestion records. This subject's data were therefore included in the analysis.

DISCUSSION

In the current study we found no impact of Malarone or primaquine on the three SUSOPS tasks (SRT, LRT, and SST) the results of which are illustrated in Figs. 1–3. Further, we did not find any impact on the multitask (Fig. 4) which assesses aviation relevant performance. In considering the possibility of a type II error, our a priori experimental design calculations indicated that 28 subjects were required to have a power of 80% to detect a difference of 4 responses/minute (about a 6% change in performance) in each of our SUSOPS tasks. This recruiting target was achieved.

We are also confident in the subset of our data that indicates neither Malarone nor primaquine impacts on subjective assessments of mood (Table IV), sleepiness, or mental or physical fatigue (Table I).

With respect to the side effect data we found a significant main effect of 'weeks' on for four of the nine

adverse effects monitored in our subjects (abdominal cramps, headache, nausea, and diarrhea). As mentioned earlier, post hoc testing has confirmed the significant main effects of 'weeks' for these four adverse effects is due to the slight rise in frequency/intensity of occurrence as reported on the last day of the 7-d drug loading protocol. At the end of the drug course, the number of subjects reporting an increase in abdominal cramps for each of the placebo, Malarone, and primaquine conditions were 7, 10, and 5 subjects, respectively. However, the small increase in abdominal cramps, was insufficient to generate either a main effect of drugs or a drug × weeks interaction, especially in view of the seven subjects complaining of abdominal cramps while on placebo. For example, if three fewer subjects had reported abdominal cramps while on placebo, the ANOVA would have generated a significant drug × weeks interaction in which post hoc testing would have confirmed Malarone had a significant impact on abdominal cramps at the end of the drug course, but not primaquine. There were no statistically significant results for the remaining five adverse effects (vomiting, anorexia, epigastric distress, dizziness, or coughing). In view of the current concern and controversy regarding the adverse effects of mefloquine (Lariam®) (2,4–6,8,11,17,28), these results are reassuring.

CONCLUSIONS

The current study found no impact of Malarone or primaquine on traditional psychomotor testing or on a complex battery simulating flying performance. Malarone or primaquine did not impact on subjective assessments of mood, sleepiness, or fatigue. There were no statistically significant differences in adverse effect rates between the medications and placebo. In this small study, Malarone and primaquine were well tolerated. These findings support the possibility of using either Malarone or primaquine for malaria chemoprophylaxis in aircrew and other occupations that demand high levels of psychomotor performance.

ACKNOWLEDGMENTS

We are indebted to Ms. Karin Kallander for assistance with the literature review and with the first draft of the ethics committee proposal.

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